

# Estimation of the Cumulated Exposure to Polychlorinated Dibenzo-*p*-dioxins/furans and Standardized Mortality Ratio Analysis of Cancer Mortality by Dose in an Occupationally Exposed Cohort

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For a cohort of 1189 male German former herbicide and insecticide workers with exposure to polychlorinated dibenzo-*p*-dioxins and -furans (PCDD/F), we report an extended standardized mortality ratio (SMR) analysis based on a new quantitative exposure index. This index characterizes the cumulative lifetime exposure by integrating the estimated concentration of PCDD/F at every point in time (area under the curve). Production department-specific dose rates were derived from blood levels and working histories of 275 workers by applying a first-order kinetic model. These dose rates were used to estimate exposure levels for all cohort members. Total mortality was elevated in the cohort; 413 deaths yielded an SMR of 1.15 (95% confidence interval [CI] 1.05, 1.27) compared to the mortality of the population of Germany. Overall cancer mortality ( $n=124$ ) was significantly increased (SMR = 1.41, 95% CI 1.17, 1.68). Various cancer sites showed significantly increased SMRs. The exposure index was used for an SMR analysis of total cancer mortality by dose. For 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD) a significant trend ( $p=0.01$ ) for the SMRs with increasing cumulative PCDD/F exposure was observed. The SMR in the first exposure quartile (0–125.2 ng/kg×years) was 1.24 (95% CI 0.82, 1.79), increasing to 1.73 (95% CI 1.21, 2.40) in the last quartile ( $\geq 2503.0$  ng/kg×years). For all congeners combined as toxic equivalencies (TEQ) using international toxic equivalency factors, a significant increase in cancer mortality was observed in the second quartile (360.9–1614.4 ng/kg×years, SMR 1.64; 95% CI 1.13, 2.29) and the fourth quartile ( $\geq 5217.7$  ng/kg×years TEQ, SMR 1.64, 95% CI 1.13, 2.29). The trend test was not significant. The results justify the use of this cohort for a quantitative risk assessment for TCDD and to a lesser extent for TEQ. — *Environ Health Perspect* 106(Suppl 2):655–662 (1998). <http://ehpnet1.niehs.nih.gov/docs/1998/Suppl-2/655-662/flesch-janys/abstract.html>

Key words: polychlorinated dibenzo-*p*-dioxins/furans, PCDD/F, occupational exposure, exposure quantification, area under the curve, cancer mortality, dose response, risk assessment

## Objectives

Although there has been a considerable amount of research on the different biochemical and health effects of 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD) and related compounds in the last 20 years, the

question whether the ubiquitous environmental presence of this substance poses any substantial health risk to humans is still a matter of scientific and public controversy. One important concern stems

from the observation that TCDD is a strong carcinogen in different animals at multiple sites (1). This is further emphasized by the results of several recent mortality studies on occupationally (2–7) or environmentally (8–10) exposed cohorts in which—in contrast to earlier studies—the exposure to TCDD was validated by measurements of its concentration in biologic material.

Several attempts have been made to estimate the magnitude of the cancer risk at environmental levels (11) or to determine a safe dose, i.e., that at which no adverse effect is expected (12,13). Available risk estimates were derived mainly from animal carcinogenicity data, especially the Kociba et al. (14) study. Results of human studies are not yet being used because of a lack of dose–response data on which to quantify the magnitude of risk at certain doses.

A first approach to quantitative analysis of a dose–response relationship on cancer was published recently (15) for a cohort of polychlorinated dibenzo-*p*-dioxins/furans (PCDD/F)-exposed workers (4). An estimate for the PCDD/F blood levels at the end of employment was derived for the whole cohort using blood-level data for a subgroup of 190 workers. From these blood levels production department-specific linear average yearly increases in PCDD/F blood concentrations (nanogram/kilogram/year) were estimated by regressing the blood levels at the end of exposure (backcalculated from the measured levels using a first order kinetic assumption) on the duration of work in different production departments. These estimates were then used to calculate the expected PCDD/F blood levels at the end of exposure for all cohort members by multiplying the working times by the estimates of the yearly increase. Using these dose parameters a dose–response relationship for cancer and exposure to PCDD/F was demonstrated.

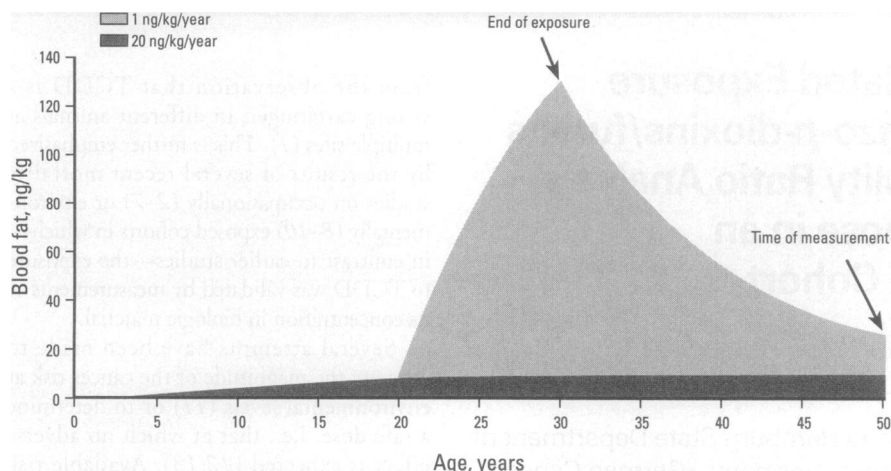
The use of these results to assess cancer risk at background levels suffers from several restrictions. First, the estimation procedure used in this former paper (15) did not take into account the elimination during exposure, which results in a nonlinear increase (Figure 1). Second, the course of the working times in different departments was not considered in the statistical model. This raises the possibility that a worker could have worked in a high-contamination area first, followed by working a long time in a department with low exposure. This would assign the worker a low blood level

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Abbreviations used: CI, confidence interval;  $\beta$ -HCH, beta-hexachlorocyclohexane; I-TEQ, international toxic equivalencies; PCDD/F, polychlorinated dibenzo-*p*-dioxins/furans; SMR, standardized mortality ratio; 2,4,5-T, 2,4,5-trichlorophenoxyacetic acid; TCDD, 2,3,7,8-tetrachlorodibenzo-*p*-dioxin; TCP, trichlorophenol; TEQ, toxic equivalencies.



**Figure 1.** Hypothetical course of TCDD blood levels for two persons with different exposures.

based on excretion at the end of exposure. Finally, the parameter blood level at the end of exposure does not appear to be appropriate for a risk assessment for dioxins with regard to background doses.

To illustrate the above situation, Figure 1 shows the course of the TCDD blood level for a hypothetical person with a dose rate of 1 ng/kg/year up to 20 years of age followed by a 10-year exposure to a dose rate of 20 ng/kg/year measured 20 years after the end of exposure compared to the course of the TCDD blood level for a person with a dose rate of 1 ng/kg/year up to 50 years of age. Several dose parameter choices are available: the maximum concentration a person experienced over time, the level at the end of exposure (not necessarily identical with the maximum concentration over time), or the integral of the concentration over time (area under the curve). The area under the curve was chosen for risk assessment analysis because it considers variations in the concentration over time and reflects cumulative lifetime exposures to dioxins and furans (16).

This paper presents basic considerations using the cohort for risk estimation and describes construction of the dose variable and a dose-response analysis relationship for cancer using the mortality of the population of Germany as a reference. A detailed dose-response analysis taking into account several covariates and coexposure, especially to beta-hexachlorocyclohexane ( $\beta$ -HCH), and an estimation of cancer risk at environmental background levels are presented by Becher et al. (17).

## Materials and Methods

The basic methods followed in this study follow Manz et al. (4) and Flesch-Janys et

al. (15). The cohort is composed of 1189 males employed on 1 January 1952 or later for at least 3 months. Follow-up ended 31 December 1992.

### Estimation of Dose Rates

Measurements of PCDD/F levels in blood ( $n = 320$ ) or adipose tissue ( $n = 62$ ) were available for 275 workers (39 females, 236 males). Two or three measurements were available for some workers, yielding a total of 382 blood samples. The blood levels were determined by the ERGO laboratory (Hamburg, Germany). Measurement methods used are described in Stephens et al. (18) and the adipose tissue concentrations are described in Beck et al. (19). The concentrations are reported in nanogram/kilogram blood or adipose fat. Toxic equivalencies (TEQs) were calculated using the international toxicity equivalency factors (I-TEFs) (20). Working histories covering the duration of employment in 22 different departments were available for the entire cohort. Categorization of the departments is described in Flesch-Janys et al. (21).

Only workers whose concentration at the time of measurement exceeded the 95% percentile of the German population

at the nearest time point for which data were available (22–24) were included in the estimation of dose rates. First, measured concentrations of each congener diminished by the median of the background concentration were backcalculated to the end of employment under the assumption of a first order elimination process. A first order kinetic equation was developed linking blood levels and working histories to produce production department-specific dose rates for every congener. Dose rates were used to estimate the concentration of every congener at every point in time for all cohort members. The cumulated PCDD/F levels expressed as nanogram/kilogram blood fat  $\times$  years were calculated by integration and used in the standardized mortality ratio (SMR) analysis. Details of this modeling procedure are presented in “Appendix.”

### Calculation of Standardized Mortality Ratios

Standardized mortality ratios were calculated using the gender-, age-, and calendar year-specific mortality rates of the German population for 1952 to 1992 (Federal Statistical Agency, Germany, personal communication). Confidence intervals (CIs) were calculated assuming the Poisson distribution for the observed cases. SMRs were estimated for the total cohort and for exposure levels categorized into four groups according to the quartiles of the calculated area under the curve above background at the end of the follow-up. Person-years were calculated taking into account the course of the person through the exposure classes. Trend tests were performed by linear regression of the SMRs on the geometric means of the exposure groups weighted by the number of observed cases (25).

## Results

### PCDD/F Blood Levels

Blood- or adipose tissue-level data were available for 275 workers. Table 1 shows

**Table 1.** Description of the TCDD and higher chlorinated PCDD/F levels (nanogram/kilogram blood fat) calculated as TEQM and TEQO, time between blood sample and end of employment for 275 workers.<sup>a</sup>

	Males ( $n = 236$ )				Females ( $n = 39$ )				Total	
	Mean	SD	Min	Max	Mean	SD	Min	Max	Mean	SD
TCDD	108.3	228.8	2.0	2252.0	110.5	281.9	6.0	1439.0	108.6	236.5
TEQO	142.0	184.0	9.7	1263.4	62.7	42.0	12.8	197.0	130.71	173.32
TEQM	247.5	339.3	11.7	2985.8	175.8	317.7	20.1	1636.0	237.3	336.6
TSEXIT	12.8	11.3	0.0	40.0	21.0	13.2	0.5	40.0	13.96	11.94

Abbreviations: Max, maximum; Min, minimum; SD, standard deviation; TEQM, international toxic equivalencies with TCDD; TEQO, international toxic equivalencies without TCDD; TSEXIT, time since end of employment (years).

<sup>a</sup>If more than one measurement was available the first was included in the calculation.

the descriptive parameters for the PCDD/F levels. The arithmetic mean for TCDD was 101.3 ng/kg (minimum, 2.0; maximum, 2252 ng/kg). For the higher chlorinated PCDD/F without TCDD calculated as international toxic equivalency (I-TEQ) the mean was 89.3 (minimum, 5.0; maximum, 1131.9). Table 2 characterizes the group with available blood levels compared to the group of workers without blood levels. The first group is slightly younger,

entered the plant later (median 1967 vs 1959), and left the plant later (median 1983 vs 1968).

Workers with blood levels had longer periods of employment than the workers without (median 9.2 vs 3 years). Table 2 also shows the distribution of workers across production departments. In general an adequate number of workers with blood levels were available, but this was not always true—especially with regard to administration

and clean-up workers. These categories were combined together from the main departments in the subsequent analysis.

### Estimation of Dose Rates

Estimated dose rates for TCDD are shown in Table 3. The highest dose rate was obtained for the trichlorophenol department before the change in production process in 1957 (3376.4 ng/kg blood fat/year). For the 2,4,5-trichlorophenoxyacetic acid

**Table 2.** Number of workers with and without data available on blood levels, age, and year at entry, of end, and duration of employment in every production department.

Variables	Workers with blood-level data				Workers without blood-level data				Total			
	no. <sup>a</sup>	$\bar{x}$	SD	$\bar{x}_{0.5}$	no. <sup>a</sup>	$\bar{x}$	SD	$\bar{x}_{0.5}$	no. <sup>a</sup>	$\bar{x}$	SD	$\bar{x}_{0.5}$
Year of birth	275	1934	10.9	1934	1314	1928	14.4	1929	1589	1929	14.1	1930
Age at entry into plant	—	30.9	10.0	29	—	32.9	11.9	31	—	32.5	11.6	30
Year of entry into plant	—	1965	9.0	1967	—	1961	8.2	1958	—	1961	8.5	1959
Year of end of employment	—	1976	10.6	1983	—	1967	10.2	1966	—	1968	10.8	1968
Duration of employment	—	10.8	8.8	9.2	—	5.9	7.7	2.3	—	6.8	8.1	3
Years in												
2,4,5-T	46	6.5	7.2	3.9	127	3.6	5.5	1.2	173	4.4	6.1	1.7
Thermic decomposition	17	8.5	6.2	8.9	15	3.5	4.6	1.3	32	6.2	6.0	3.2
TCP before 1957	21	1.3	1.2	0.7	75	0.9	1.1	0.4	96	0.9	1.1	0.5
TCP after or during 1957	35	6.2	6.3	3.6	92	3.9	4.8	1.8	127	4.5	5.4	2.3
Trichlorobenzene	18	2.1	2.3	1.6	80	1.3	2.4	0.4	98	1.4	2.4	0.5
Bromophos	15	9.1	6.1	9.2	34	3.6	4.0	2.3	49	5.3	5.3	3.4
HCH synthesis	33	4.6	5.8	1.65	86	4.1	6.6	0.8	119	4.2	6.4	1.0
Lindane	67	5.4	6.0	2.4	338	3.4	6.2	1.0	405	3.8	6.2	1.0
Formulation	59	3.9	5.6	1.5	384	2.5	4.5	0.8	443	2.7	4.7	0.9
Metal workers	27	12.2	8.8	9.5	64	6.4	7.6	3.0	91	8.1	8.4	4.1
Other manual workers	20	9.2	8.1	5.8	41	6.5	7.3	3.7	61	7.4	7.6	4.4
Unskilled workers	26	0.9	2.9	0.2	152	0.9	2.5	0.2	178	0.9	2.6	0.2
Storage and transport	34	6.1	6.9	3.9	149	6.1	7.9	2.2	183	6.1	7.7	2.8
Laboratory	15	8.8	9.5	3.5	49	5.9	7.6	3.5	64	6.6	8.1	3.5
Engineers	10	9.7	7.9	8.9	35	8.6	8.0	5.0	45	8.8	7.9	6.2
Opiate	26	4.7	5.8	2.1	136	3.6	4.7	1.3	162	3.7	4.9	1.4
Kitchen	3	1.5	0.7	1.6	50	4.5	4.6	2.6	53	4.4	4.5	2.3
Administration	3	13.2	4.4	13.8	53	11.2	10.2	8.4	56	11.3	10.0	8.5
Plant security	5	17.5	7.3	14.4	24	6.5	5.7	6.0	29	8.4	7.2	6.7
Laundry	11	7.9	6.4	7	34	5.0	5.9	2.7	45	5.7	6.1	4.2
Clean-up administration	3	8.4	11.1	2.7	29	5.8	5.2	5.1	32	6.0	5.7	4.5
Others/unclassified	4	8.1	12.5	2.6	29	2.2	2.5	1.1	33	2.9	4.9	1.1

Abbreviations: 2,4,5-T, trichlorophenoxyacetic acid; TCP, trichlorophenol. <sup>a</sup>Multiple counts.

**Table 3.** Estimated dose rates (nanogram/kilogram blood fat/year) for TCDD and TEQs without TCDD) for PCDD/Fs, and  $\beta$ -HCH for different production departments.

Production department	TCDD	95% CI	TEQ	95% CI	$\beta$ -HCH	95% CI
Trichlorophenol before 1957	3376.4	2261.4–4491.4	90.0	15.1–164.8	14.6	4.1–25.1
2,4,5-Trichlorophenoxyacetic acid	154.6	102.5–206.7	33.8	7.8–59.8	1.7	–5.3–8.7
Trichlorophenol after or during 1957	121.1	63.9–178.3	35.9	8.8–62.9	14.6	4.1–25.1
Manual workers	48.2	10.6–85.8	34.4	18.1–50.6	13.6	6.4–28.8
Bromophos	30.2	–6.8–64.2	15.1	1.4–28.8	10.4	–1.0–21.9
Hexachlorocyclohexane synthesis	30.2	–6.8–64.2	15.1	1.4–28.8	31.9	21.5–42.3
Formulation	30.2	–6.8–64.2	15.1	1.4–28.8	12.7	1.3–24.1
Unskilled workers	30.2	–6.8–64.2	15.1	1.4–28.8	8.4	1.6–15.1
$\alpha$ -Decomposition/trichlorobenzene	6.7	–17.6–31.0	116.6	90.2–142.9	46.5	33.1–60.0
Lindane	6.7	–17.6–31.0	15.9	–5.2–36.9	17.7	10.6–24.8
Storage and transport	6.7	–17.6–31.0	29.2	2.0–56.4	8.4	1.6–15.1
Laboratory, engineers	6.7	–17.6–31.0	15.1	1.4–28.8	1.7	–5.3–8.7
Opiate (morphin production)	6.7	–17.6–31.0	15.1	1.4–28.8	8.4	1.6–15.1
Kitchen	6.7	–17.6–31.0	15.1	1.4–28.8	0	—
Laundry	6.7	–17.6–31.0	15.1	1.4–28.8	31.6	15.5–47.7
Administration, clean-up	0	—	0	—	0	—
Plant security, others	0	—	0	—	1.7	–5.3–8.7

(2,4,5-T) and trichlorophenol (TCP) departments after 1957 the dose rates were of the same order of magnitude (154.6 and 121.1 ng/kg blood fat/year). For manual workers the estimate was 48.2. All these estimates were significantly different from zero ( $p \leq 0.01$ ). According to the magnitude of the estimates in the model with all 22 production departments (data not shown), the other departments were grouped into 2 groups, with estimated dose rates of 30.2 and 6.7 ng/kg/year. One metalworker and two workers in the TCP department, identified as outliers by regression diagnostics, were excluded from the final model. The dose rate estimates for TCDD for metalworkers were decreased from 184 ng/kg/year to 48.2 ng/kg/year by this exclusion and that for the TCP department before 1957 decreased from 3781.3 ng/kg/year to 3376.4 ng/kg/year. Except for TCP, no production period-specific differences in the estimated dose rate could be identified for any department. However,

the data for different time periods were sparse. No gender-specific effect or effects of short durations of employment on dose rates were seen. Data for these latter analyses were also sparse.

Figure 2, which illustrates the fit of the model, compares TCDD concentrations at the end of employment calculated from the measured levels (using "Appendix" equation 3) with TCDD concentrations predicted by the model. The symbols indicate different lengths of employment. The Spearman rank correlation coefficient for comparison of the estimated with the measured levels was 0.53.

Estimated dose rates for the higher chlorinated congeners without TCDD expressed as I-TEQs are shown in Table 3. Highest dose rates were observed for the thermic decomposition department (116.6 ng/kg/year; 95% CI 90.2, 142.9). The TCP production department yielded a dose rate of 90.0 ng/kg/year (95% CI 15.1, 164.8) for the time before 1957—mainly driven by

a high estimate for pentadioxin—and 35.9 ng/kg/year (95% CI 8.8, 62.9) thereafter. For manual workers the estimate was 34.4 ng/kg/year (95% CI 18.1, 50.6). Estimates for the other departments ranged from 0 for administration to 33.8 ng/kg/year for the 2,4,5-T department.

No dose rates were calculated for 2,3,7,8-tetrachlorodibenzofuran, 1,2,3,7,8-pentachlorodibenzofuran, and octachlorodibenzofuran because of the lack of a half-life estimate (26). However, the blood levels of these congeners generally were within the range of the ubiquitous background levels and did not contribute substantially to the total TEQs. The Spearman rank correlation coefficients for the higher chlorinated congeners varied between 0.26 for heptadioxin and 0.60 for 1,2,3,4,7,8,9-hepta-furan.

For  $\beta$ -HCH the highest dose rate was estimated for the thermic decomposition department (46.5  $\mu$ g/liter blood/year; 95% CI 33.1, 60.0), followed by the

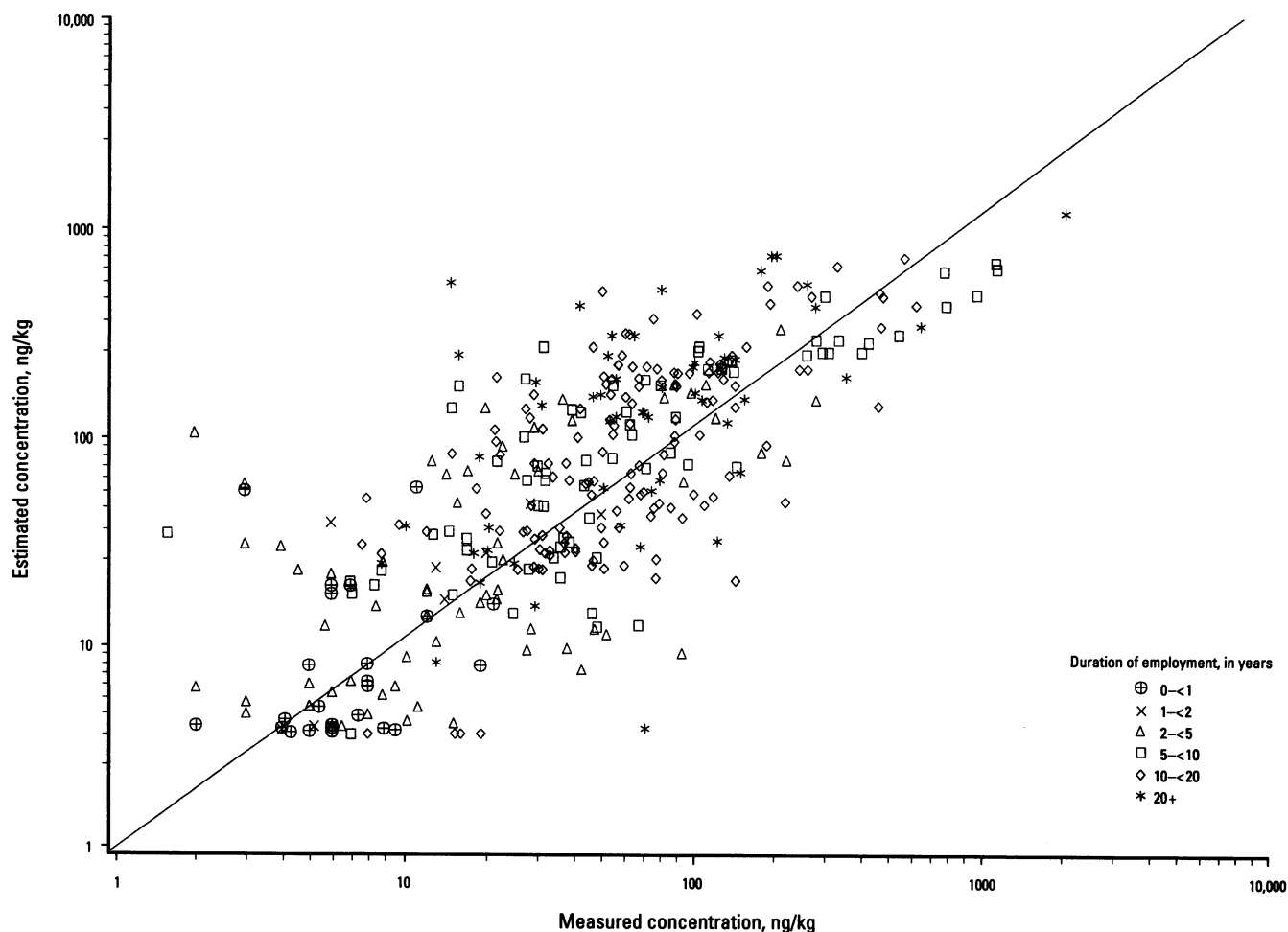


Figure 2. Observed and estimated TCDD levels by duration of employment.

department for the synthesis of HCH (31.9 µg/liter blood/year; 95% CI 21.5, 42.3). There was a high estimate for the laundry department as well (31.6 µg/liter blood/year; 95% CI 15.5, 47.7), but this was based on only four measurements. Estimates for the other departments ranged between 0 for administration and 17.7 µg/liter blood/year for the lindane department. The Spearman rank correlation coefficient was 0.72 ( $p < 0.01$ ). Figure 3 shows the estimated time/concentration curve for one of the cohort members.

### Standardized Mortality Ratio Analysis

Table 4 shows SMRs for different causes of death for the total cohort. Total mortality was significantly elevated (SMR 1.15; 95% CI 1.05, 1.27). A total of 124 cancer deaths yielded a significantly elevated SMR (1.41; 95% CI 1.17, 1.68) produced by elevations of several localizations. Statistically significant elevations were observed for rectum (SMR 2.3; 95% CI 1.05, 4.37), lung (1.51; 95% CI 1.07, 2.08), other respiratory cancers including mesotheliomas (1.71; 95% CI 1.24, 2.29), and all hematopoietic and lymphatic cancers (2.16; 95% CI 1.11, 3.77), especially lymphosarcoma (3.73; 95% CI 1.20, 8.71). The SMRs for several other localizations were nonsignificantly increased; these included the esophagus (2.36; 95% CI 0.76, 5.50), larynx (3.10; 95% CI 0.83, 7.94), and prostate (1.47; 95% CI 0.67,

2.78). Estimates for several localizations were below 1; however, with the exception of colon cancer, these generally were not localizations with large numerical impacts on total cancer mortality.

The SMR for cardiovascular diseases was slightly nonsignificantly elevated (1.06; 95% CI 0.90, 1.24). No increase was observed for nonmalignant respiratory diseases or for digestive diseases. The SMR for unnatural causes (accidents and suicides) was 1.79 (95% CI 1.35, 2.33). There were 24 ill defined or unknown causes of death, yielding an SMR of 2.59 (95% CI 1.66, 3.85).

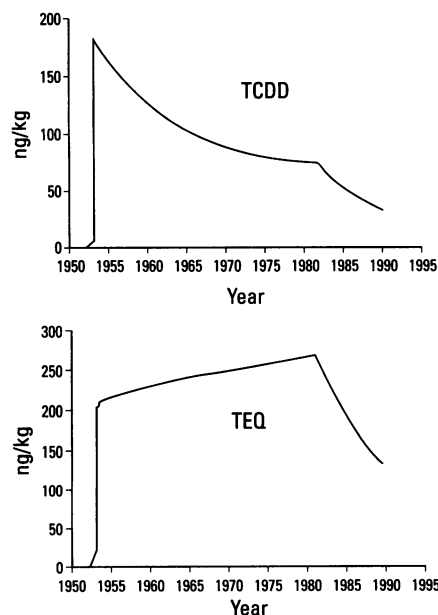
Table 5 shows the results of the SMR analysis using the estimated integrated TCDD concentration until the end of follow-up as dose parameter. A U-shaped relation between dose and mortality was

observed for all causes of death. The linear trend test was not significant. The SMR for all cancer combined was 1.24 (95% CI 0.82, 1.79) for the first quartile (up to 125.2 ng/kg blood fat × year) and increased from 1.34 in the second and third to 1.73 (95% CI 1.21, 2.40) in the fourth quartile (more than 2503.0 ng/kg × year). The linear trend test was significant ( $p = 0.013$ ). No trend was observed for lung cancer or for all hematopoietic and lymphatic cancers combined. Total TEQs also showed a U-shaped relation to total mortality (Table 6). For total cancer the SMR in the first quartile (up to 360.9 ng/kg × year) was 1.07 (95% CI 0.69, 1.58). A significant increase was observed in the second quartile (1.64; 95% CI 1.13, 2.29), which ranged up to 1614.4 ng/kg × years. The

**Table 4.** Standardized mortality ratios for selected causes of death using the mortality rates of the population of Germany as reference.

ICD-9	Cause of death	O	E	SMR	95% CI
10-999	All causes <sup>a</sup>	413	357.71	1.15	1.05-1.27
10-139	Infections	2	4.91	0.41	0.05-1.47
140-208	Malignancies of:	124	88.12	1.41	1.17-1.68
140-149	Buccal cavity, pharynx	3	2.17	1.38	0.28-4.04
150	Esophagus	5	2.12	2.36	0.76-5.50
151	Stomach	13	10.88	1.19	0.64-2.04
153	Colon	2	6.21	0.32	0.04-1.16
154	Rectum	9	3.91	2.30	1.05-4.37
155	Liver, gall bile	2	2.77	0.72	0.09-2.61
157	Pancreas	3	3.88	0.77	0.16-2.26
161	Larynx	4	1.29	3.10	0.83-7.94
162	Lung	38	25.11	1.51	1.07-2.08
162-165	Respiratory	44	25.75	1.71	1.24-2.29
170	Bone	0	0.49	0.00	-
171	Soft tissue	0	0.33	0.00	-
172-173	Skin	2	1.02	1.96	0.24-7.08
174-175	Breast	0	0.12	0.00	-
185	Prostate	9	6.14	1.47	0.67-2.78
188	Bladder	2	2.90	0.69	0.08-2.49
189	Kidney	5	2.57	1.95	0.63-4.54
191-192	Brain	3	1.57	1.91	0.39-5.58
193	Thyroid	0	0.31	0.00	-
194	Endocrine gland	1	0.10	10.00	0.25-55.72
195	Ill-defined	5	4.25	1.18	0.38-2.75
200-208	Lymphatic and hematopoietic cancer	12	5.56	2.16	1.11-3.77
200	Lymphosarcoma	5	1.34	3.73	1.20-8.71
201	Morbus Hodgkin	0	0.79	0.00	-
203	Multiple myelomas	3	0.70	4.29	0.88-12.52
204-208	Leukemia	4	2.63	1.52	0.41-3.89
290-319	Psychiatric	3	3.57	0.84	0.17-2.46
320-389	Nervous system	7	8.26	0.85	0.34-1.75
390-459	Cardiovascular	156	146.92	1.06	0.90-1.24
410-414	Ischemic	76	78.17	0.97	0.77-1.22
430-438	Cerebrovascular	24	32.07	0.75	0.48-1.11
460-519	Respiratory	13	23.34	0.56	0.30-0.95
520-579	Digestive	23	24.99	0.92	0.58-1.38
780-799	Ill defined <sup>b</sup>	24	9.28	2.59	1.66-3.85
800-999	Unnatural causes	56	31.23	1.79	1.35-2.33

Abbreviations: E, expected number of cases; ICD-9, *International Classification of Diseases, Ninth Revision* (World Health Organization, Geneva); O, observed. <sup>a</sup>In contrast to an earlier paper (Flesch-Janys et al. (15)), one cause of death was not counted in the cause-specific SMR analysis because of unreliable cause-of-death statistics for age groups > 85 years. <sup>b</sup>Including unknown causes of death.



**Figure 3.** Estimated concentration over time for TCDD and TEQ for one cohort member.

**Table 5.** Standardized mortality ratios for selected causes of death by TCDD quartiles above background levels.

ICD-9	Cause of death	TCDD quartile <sup>a</sup>	O	E	SMR	95% CI	p, trend
000-E999	All causes	I	120	94.80	1.27	1.05-1.51	0.66
		II	107	89.20	1.20	0.98-1.45	
		III	83	93.26	0.89	0.71-1.10	
		IV	103	80.46	1.28	1.04-1.55	
		All	413	357.72	1.15	1.05-1.27	
140-208	Total cancer	I	28	22.57	1.24	0.82-1.79	0.01
		II	29	21.64	1.34	0.90-1.92	
		III	31	23.17	1.34	0.91-1.90	
		IV	36	20.75	1.73	1.21-2.40	
		All	124	88.12	1.41	1.17-1.68	
162	Lung cancer	I	10	6.39	1.56	0.75-2.88	0.61
		II	10	6.13	1.63	0.78-3.00	
		III	8	6.56	1.22	0.53-2.40	
		IV	10	6.03	1.66	0.79-3.05	
		All	38	25.11	1.51	1.07-2.08	
200-208	Hematopoietic and lymphatic cancer	I	4	1.57	2.55	0.69-6.52	0.17
		II	3	1.36	2.21	0.45-6.45	
		III	4	1.38	2.90	0.78-7.42	
		IV	1	1.25	0.80	0.02-4.46	
		All	12	5.56	2.16	1.11-3.77	

<sup>a</sup>I, 0 ≤ TCDD < 125.2; II, 125.2 ≤ TCDD < 627.1; III, 627.1 ≤ TCDD < 2503.0; IV, 2503.0 ≤ TCDD.

**Table 6.** Standardized mortality ratios for selected causes of death by TEQ quartiles above background levels.

ICD-9	Cause of death	TEQ quartile <sup>a</sup>	O	E	SMR	95% CI	p, trend
000-E999	All causes	I	121	97.92	1.24	1.03-1.48	0.67
		II	100	84.99	1.18	0.96-1.43	
		III	92	94.86	0.97	0.78-1.19	
		IV	100	79.95	1.25	1.02-1.52	
		All	413	357.71	1.15	1.05-1.27	
140-208	Total cancer	I	25	23.32	1.07	0.69-1.58	0.48
		II	34	20.78	1.64	1.13-2.29	
		III	31	23.26	1.33	0.91-1.89	
		IV	34	20.76	1.64	1.13-2.29	
		All	124	88.12	1.41	1.17-1.68	
162	Lung cancer	I	8	6.62	1.21	0.52-2.38	0.85
		II	13	5.92	2.20	1.17-3.76	
		III	6	6.55	0.92	0.33-1.99	
		IV	11	6.02	1.83	0.91-3.27	
		All	38	25.11	1.51	1.07-2.08	
200-208	Hematopoietic and lymphatic cancer	I	5	1.64	3.05	0.98-7.11	0.44
		II	2	1.33	1.50	0.18-5.43	
		III	3	1.35	2.22	0.46-6.49	
		IV	2	1.23	1.63	0.20-5.87	
		All	12	5.56	2.16	1.11-3.77	

<sup>a</sup>I, 0 ≤ TEQ < 360.9; II, 360.9 ≤ TEQ < 1614.4; III, 1614.4 ≤ TEQ < 5217.7; IV, 5217.7 ≤ TEQ.

estimate for the third quartile was 1.33 (95% CI 0.91, 1.89) and it increased to 1.64 (95% CI 1.13, 2.29) in the fourth quartile (> 5217.7 ng/kg×years). The linear trend test for all cancer was not significant ( $p = 0.48$ ). This was also true for lung cancer and hematopoietic and lymphatic cancers.

## Discussion

A significant 40% increase in total cancer mortality was observed for the whole cohort compared to that for the German population. Thus, cancer mortality increased in the 3 additional years of follow-up (1989 to 1992) from 1.24 to 1.41. This elevation in total cancer mortality was not restricted to

one localization. Significant increases were observed for lung, all respiratory cancers, rectum, and hematopoietic and lymphatic cancers, especially lymphosarcomas, which belong to the non-Hodgkin's type of lymphomas. No case of soft-tissue sarcoma was observed, although 0.33 were expected.

Available blood levels revealed the cohort had substantial exposure to TCDD. Mean concentration at the time of measurement was 101.3 ng/kg TCDD, with a maximum level of 2252 ng/kg. There was also substantial exposure to higher chlorinated congeners, with a mean of 89.3 ng/kg TEQ (without TCDD) and a maximum of 1131.9 ng/kg.

Estimated dose rates derived from these measurements allowed estimation of the maximal concentration for each worker during his or her period of observation. For TCDD a mean of 340.5 ng/kg was observed. Highest concentrations were estimated for three workers with values between 10,000 and 13,000 ng/kg. The mean of the estimated maximum concentrations for total I-TEQ was 473.5 ng/kg, with a maximum value of 13,179 ng/kg I-TEQ.

With the exception of  $\beta$ -HCH [see Becher et al. (17)], other potential confounders like smoking habits and exposure to other carcinogenic or suspected carcinogenic substances could not be addressed directly. With regard to smoking, we showed that blood-level estimates were not correlated with smoking status for a subgroup of workers (15) for whom these data were available. In addition, calculating total cancer mortality without lung cancer cases for the TCDD exposure groups yielded an even more pronounced trend (SMRs for TCDD quartiles I-IV: 1.11, 1.23, 1.38, and 1.77, calculated from Table 5) in contrast to what one would expect if smoking had been a strong confounder of the observed dose-response relationship. We showed that exposure to other carcinogens occurred mainly in departments with low exposure to TCDD [Flesch-Janys et al. (15)].

An important question in dose-response analysis is whether exposure measurements reflect the exposure of all cohort members with sufficient accuracy. First, the relationships between the production department-specific estimates are in good agreement with the expectation from the chemistry of the production processes and the available data on the contamination of products, buildings, and waste. The highest dose rates for TCDD were obtained for the 2,4,5-T and 2,4,5-TCP departments, as expected. Measurements indicate contamination of 2,4,5-T acid in the parts per million range in former years, whereas in waste from 2,4,5-T production concentrations up to 3360  $\mu\text{g/kg}$  TCDD were detected. In contrast, the octachlorodibenzodioxin concentrations of up to 7200  $\mu\text{g/kg}$  were comparably low. Conversely, the highest dose rates for the higher chlorinated congeners were obtained for the thermic decomposition department, where measurements of smelting showed hexa- and octadioxin concentrations up to  $32 \times 10^6$   $\mu\text{g/kg}$  but only 500  $\mu\text{g/kg}$  TCDD (21). For this department the highest dose rates for the higher chlorinated congeners were detected.

For some departments we observed positive but nonsignificant dose rates. We were aware of the possibility of overfitting the model; however, the estimates were all in good agreement with a priori knowledge of exposure levels so we decided to use them. No information was available on job duties within the departments or on potential accidental exposure. These factors could yield some additional variations.

Another critical point is the assumption of a first order elimination kinetic. Available human data (26,27) indicate that this assumption is reasonable, at least in the observed dose range. No human data were available on the form of absorption kinetics that could have been considered in the exposure model. There were few workers with short durations of employment and comparably high levels of PCDD/F. Whether this could be attributed to individual exposure histories, i.e., accidental or time/concentration-dependent modulation of PCDD/F absorption, remains unclear.

SMR analysis revealed a significant trend for total cancer mortality with increasing estimated cumulated TCDD levels. This result is supported by a study from the Netherlands (28) and the latest results on cancer mortality within an accidental German cohort (5). The dose estimates in the Netherlands study indirectly support the dose-rate estimation presented in this paper in that the Netherlands results were roughly in the same order of magnitude, though a different estimation technique was used. For total TEQ the trend was not as pronounced as for TCDD.

In summary, we observed an elevated risk of total cancer mortality in a cohort with high exposure to PCDD/F. A dose-dependent effect was observed for estimated TCDD levels on total cancer mortality by SMR analysis using an index that characterizes cumulated exposure to TCDD and the higher chlorinated congeners. We conclude that use of these data for quantitative cancer risk assessment is justified.

## Appendix

Estimation of the dose rates was performed in the following steps:

1. For every congener only those individuals were included whose blood levels exceeded the 95% CI of the German background concentrations (22–24).

2. The median of the background concentration was subtracted from the measured levels.

3. Assuming a first order kinetic model for every individual included the background-adjusted levels  $y_n$  taken at time  $t_{M(n)}$  were backcalculated to the date of exit from the plant  $t_{A(n)}$  according to the formula:

$$y_n(t_{A(n)}) = y_n(t_{M(n)}) \times \exp[\lambda(n) \times (t_{M(n)} - t_{A(n)})],$$

where  $n$  denotes the individuals ( $n = 1, \dots, N$ ) ( $N = 275$ ). The decay parameters  $\lambda(n)$  for the different congeners and for  $\beta$ -HCH were derived from the results of a half-life study within a subgroup of  $n = 48$  workers with two or three measurements at different time points (26,29). Decay rates adjusted for age and percent body fat were used.

4. To estimate the department-specific dose rates, a linear regression model without an intercept was specified as follows:

$$E(y_n(t_{A(n)})) = \sum_{i=1}^m \mu_i f_i \quad n = 1, \dots, N$$

with

$$f_i = \frac{1}{\lambda} \sum_{j=1}^k [1 - \exp(-\lambda(t_{Aij} - t_{Eij}))] \times \exp[-\lambda(t_{A(n)} - t_{Aij})],$$

where  $\mu_i$ ,  $i = 1, \dots, m$  denotes the dose rate for the  $m$  different departments where a worker could have worked up to  $k$  times. The working time ( $j$ ) in the department ( $i$ ) started at time  $t_{Eij}$  and ended at  $t_{Aij}$ . In this model it was assumed that the dose rate for a specific department was constant over time.

5. To identify relevant departments the following procedure was performed: First, for every congener, models, including all departments separately, were fitted. Second, the potential impacts of gender and different production periods were tested by including appropriate dummy variables. Third, three outliers were identified by regression diagnostics and excluded (30). These observations changed the effect estimate by more than 10%. The exclusion was further supported by industrial hygiene data. Fourth, departments for which estimates showed large standard errors were combined into two groups. This grouping was guided by the magnitude of the estimates and a priori plausibility considerations on the expected exposure to PCDD/F from the chemistry of the processes. For all higher chlorinated congeners except PCDD, the same grouping was used. Fifth, the Spearman rank correlation coefficient was used as a descriptive measure for the model fit because the Pearson correlation coefficient was affected by some large residuals.

6. The estimated dose rates  $\mu_i$  were then used to estimate the blood level at every point in time as follows:

$$y(t) = \sum_{i=1}^m \frac{\mu_i}{\lambda} \sum_{j=1}^k \left[ (1 - \exp(-\lambda(t_{Aij} - t_{Eij}))) \times \exp(-\lambda(t - t_{Aij})) I_{\{t > t_{Aij}\}}(t) + (1 - \exp(-\lambda(t_{Aij} - t_{Eij}))) \times I_{\{E_{ij} \leq t < t_{Aij}\}}(t) \right],$$

$I$  represents the indicator function.

7. The area under the curve was calculated as

$$D(t) = \int_{t_E}^t y(x) dx,$$

where  $t_E$  denotes the date of entry into the plant and  $t$  the date of end of observation, which can be solved by elementary integration rules.

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